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Relationship Between Severity of Fibrinolysis Based on Rotational Thromboelastometry and Conventional Fibrinolysis Markers

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Abstract

The association between severity of fibrinolysis, ascertained by rotational thromboelastometry to diagnose hyperfibrinolysis in patients with out-of-hospital cardiac arrest (OHCA), and conventional fibrinolysis markers (ie, tissue-plasminogen activator [t-PA], plasminogen, α_2-plasmin inhibitor [α_2-PI], and plasminogen activator inhibitor [PAI]) with key roles in the fibrinolytic system was investigated. This prospective observational study included 5 healthy volunteers and 35 patients with OHCA from the Hokkaido University Hospital. Blood samples were drawn immediately upon admission to the emergency department. Assessments of the extrinsic pathway using tissue factor activation (EXTEM) and of fibrinolysis by comparison with EXTEM after aprotinin addition (APTEM) were undertaken. Conventional coagulation and fibrinolysis markers were measured in the stored plasma samples. Significant hyperfibrinolysis observed in EXTEM disappeared in APTEM. Patients exhibited significantly higher levels of fibrinogen/fibrin degradation products, plasmin–α_2-PI complex, and t-PA but lower levels of fibrinogen, plasminogen, and α_2-PI than healthy controls. The PAI level was unchanged. Fibrinolytic parameters of EXTEM correlated with levels of lactate and conventional fibrinolysis markers, especially t-PA. Increased t-PA activity and decreased plasminogen and α_2-PI significantly correlated with increased severity of fibrinolysis (hyperfibrinolysis).

Keywords

hyperfibrinolysis, out-of-hospital cardiac arrest, rotational thromboelastometry, tissue plasminogen activator, α_2-plasmin inhibitor

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Introduction

Prolonged systemic ischemia after cardiac arrest and recirculation following the return of spontaneous circulation (ROSC) induces global tissue and organ injury. This unique condition constitutes the main pathophysiological state of patients with out-of-hospital cardiac arrest (OHCA).[1] Dynamic changes in the coagulation and fibrinolytic system were observed during and immediately after resuscitation in patients who experienced OHCA. The activation of the coagulation cascade was observed as an elevation in the levels of soluble fibrin,[2,3] fibrinopeptide A,[4] tissue factor antigen,[5] and the thrombin–antithrombin complex[6] in patients with OHCA. However, few investigations of fibrinolytic changes in patients with OHCA have been reported.[2-4,7] An early report demonstrated that hyperfibrinolysis was associated with an elevation in tissue-plasminogen activator (t-PA) antigens and t-PA activity in patients with OHCA on arrival at the emergency department.[4] Moreover, hyperfibrinolysis was evidenced through high levels of the plasmin–α2 plasmin inhibitor complex (PIC),[2,3]

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d-dimer,[2-4] and fibrin/fibrinogen degradation products (FDPs)[3,7] in patients with OHCA. However, these abovementioned investigations did not evaluate the association of conventional markers of fibrinolysis with findings on a viscoelastic analysis.[2-4,7]

Rotational thromboelastometry (ROTEM; TEM International GmbH) comprises a point-of-care device that measures the viscoelastic properties of whole blood samples and presents a graphical display of the viscoelasticity processes from the initiation of clotting to clot retraction and fibrinolysis. Viscoelastic devices, such as ROTEM, are widely used in various clinical situations, such as liver transplantation,[8,9] trauma,[10-12] postpartum hemorrhage,[13,14] and cardiac surgery[15,16] as well as in patients who have sustained a cardiac arrest.[17-20] In previous studies, hyperfibrinolysis in patients with OHCA was frequently diagnosed by ROTEM.[17-21] Hyperfibrinolysis was defined by maximum lysis, which indicated a percentage decrease in clot firmness from maximum clot firmness during the observation time and lysis onset time (LOT), which indicated time (in seconds) from the start of clotting (clotting time) to the initiation of clot lysis.[17-21] Furthermore, hyperfibrinolysis was associated with base excess,[17] lactate levels,[17,18] and cardiopulmonary resuscitation time.[18] However, these studies did not evaluate the association of ROTEM parameters with conventional fibrinolytic variables.[17-21]

A detailed association between conventional coagulofibrinolytic variables and ROTEM parameters remains unclear. Therefore, we conducted this study to evaluate the relationship between the severity of fibrinolysis based on ROTEM and conventional fibrinolysis markers, especially t-PA, plasminogen (PLG), α_2-plasmin inhibitor (α2-PI), and total plasminogen activator inhibitor (PAI), in patients with OHCA.

Materials and Methods

Patient Selection

Ethical approval for this study was obtained from the Institutional Review Board of the Ethics Committee of Hokkaido University Hospital. Written informed consent was obtained from the patients or their next of kin. The study included 35 patients with OHCA on hospital arrival between April 2012 and July 2015. Patients with cardiac arrest due to trauma, infection, aortic dissection, or massive bleeding were excluded.

Measurements

Blood samples were immediately drawn from patients with OHCA on admission to the emergency department. Blood samples collected from 5 healthy adult volunteers served as controls. All blood samples were centrifuged at 3000 rpm for 5 minutes at 4 °C. Plasma samples were stored at −80 °C until further analyses. We undertook assessments of the extrinsic pathway using tissue factor activation (EXTEM) and of fibrinolysis by comparison with EXTEM after the addition of aprotinin (APTEM) in ROTEM for 3 hours. We measured conventional markers of coagulation and fibrinolysis in the stored plasma samples.

Table 1. Characteristics of Patients With Cardiac Arrest.[a]

Characteristics	n = 35
Age, year	76 (62 to 84)
Men, n (%)	16 (46)
Origin of cardiac arrest	
Cardiac, n (%)	21 (60)
Noncardiac, n (%)	14 (40)
Witnessed by a bystander, n (%)	18 (53)
Duration of cardiac arrest, min	36 (29 to 41)
Blood gas analysis	
pH	6.838 (6.762 to 6.971)
Base excess, mmol/L	−20.0 (−23.1 to −17.6)
Lactate, mmol/L	13.6 (11.0 to 15.0)

[a]Data are presented as median (interquartile range) unless stated otherwise.

Analysis of ROTEM

Thromboelastometry measures the change in the viscoelasticity of blood as it coagulates when it comes in contact with an extraneous substance and was first proposed by Hartert.[22] The ROTEM analyzer uses a fixed cuvette with an axis that oscillates continuously. A total of 300 μL whole blood with activators is placed into the cuvette such that the tip of the pin, fixed on a steel axis, is immersed in the test solution. The central portion of the axis is guided with shaft bearings, and the pin is rotated by a spring connector that alternates between the right and left sides. The movement of the axis is detected by using an optical detection system that comprises a mirror plate on the steel axis, a light-emitting diode, and a charge-coupled device camera, and the findings were analyzed using a computer that was equipped with a dedicated software program.[23]

The ROTEM test includes the EXTEM and APTEM tests.[1] The EXTEM test is an extrinsic coagulation test that is primed with the rabbit brain tissue factor. The APTEM test uses tissue factor and antifibrinolytic aprotinin as reagents and evaluates fibrinolysis by comparing it with EXTEM. The ROTEM parameters include clotting time, clot formation time, maximum clot firmness, α angle, lysis index at time 30 minutes, maximum lysis, LOT, and lysis time. The implications of these variables is summarized in Supplementary Table 1.

Conventional Coagulation Parameters

The conventional coagulofibrinolytic variables that were measured include fibrinogen, fibrinogen/fibrin degradation products, PLG, α_2-PI, PIC, PAI, and prothrombin time. These variables were measured at the Central Laboratory for Clinical Chemistry. The t-PA activity was measured using a commercial Chromogenic Activity kit (Human tPA Chromogenic Activity Kit, Assaypro LLC).

Table 2. Results of Thromboelastometry and Conventional Laboratory Tests.[a]

Thromboelastometry and conventional laboratory tests	Control n = 5	Cardiac arrest n = 35	*P* value
EXTEM test			
Clotting time, seconds	103 (94-109)	73 (53-89)	.024
Clot formation time, seconds	66 (61-68)	107 (83-136)	.008
Maximum clot firmness, mm	64 (63-66)	55 (48-63)	.047
α Angle, degree	76 (76-77)	69 (65-76)	.086
Lysis index at time 30 minutes, %	99 (99-99)	96 (4-100)	.605
Maximum lysis, %	25 (23-27)	100 (100-100)	<.001
Lysis onset time, seconds	4513 (4188-4618)	1961 (1107-3397)	.001
Lysis time, seconds	ND	2550 (1352-4471)	NA
APTEM test			
Clotting time, seconds	72 (67-77)	77 (69-83)	.310
Clot formation time, seconds	93 (89-96)	109 (81-136)	.310
Maximum clot firmness, mm	63 (60-64)	59 (55-66)	.475
α Angle, degree	73 (73-74)	69 (64-76)	.475
Lysis index at time 30 minutes, %	99 (99-100)	100 (100-100)	.031
Maximum lysis, %	22 (21-24)	12 (8-16)	<.001
Conventional laboratory test			
Fibrinogen, mg/dL	259 (254-264)	105 (81.5-158.5)	.002
Fibrinogen/fibrin degradation products, μg/mL	2.7 (2.5-3.1)	2572 (1953-3330.5)	<.001
Plasminogen, %	96 (94-101)	24 (17-30)	<.001
α_2-plasmin inhibitor, %	98 (96-99)	10 (10-13)	<.001
Plasmin-α_2-plasmin inhibitor complex, μg/mL	0.5 (0.4-0.5)	93.6 (79.35-108.05)	<.001
Total plasminogen activator inhibitor, ng/mL	18 (16-20)	25 (16-46)	.157
Prothrombin time, seconds	11.4 (10.8-11.7)	26.65 (19.25-36.25)	<.001
Tissue-plasminogen activator, IU/mL	109 (55-150)	28 260 (21 040-29 740)	<.001

Abbreviations: EXTEM test, the extrinsic coagulation test that is primed using rabbit brain tissue factor; APTEM test, consists of the EXTEM test in the presence of the antifibrinolytic aprotinin; NA, not available; ND, not detected.
[a]Data are presented as median (interquartile range).

Statistical Analyses

All measurements are expressed as medians (interquartile ranges). The IBM SPSS 25 (IBM Japan) was used for statistical analyses and calculations. Comparisons between the 2 study groups were undertaken with the Mann-Whitney *U* test. The correlation between the 2 measurements was investigated using Spearman correlation analysis. The study population was divided into 4 groups according to the severity of fibrinolysis, based on the LOT quartile in the EXTEM tests. The Jonckheere-Terpstra test was used to analyze an ordered difference in each group. The level of significance was set at $P < .05$.

Results

The characteristics of the patients with OHCA are shown in Table 1. Severe lactic acidosis was observed in all patients with OHCA. Blood samples were drawn from 25 patients during cardiopulmonary resuscitation after arrival at the emergency department, and immediately after the ROSC in the emergency department in 10 patients. In patients in whom the blood samples were obtained during cardiopulmonary resuscitation, the duration of cardiac arrest was defined as the duration from cardiac arrest to blood sampling. The results of thromboelastometry and conventional laboratory tests in the control group and in patients with OHCA are presented in Table 2. In patients with OHCA, a significant level of fibrinolysis was observed on the results of the EXTEM test; however, hyperfibrinolysis was normalized in the results of the APTEM test. In conventional laboratory tests, patients with OHCA exhibited significantly higher levels of FDP, PIC, and t-PA activity, and lower levels of PLG and α_2-PI than in the control group. The conventional laboratory test findings indicated fibrinolysis levels to be the same as those in the results of the EXTEM test.

The correlation of fibrinolytic variables (ie, lysis index at time 30 minutes, LOT, and lysis time in the EXTEM test) with other variables in patients with OHCA is presented in Table 3. The lysis index at time 30 minutes, LOT, and lysis time correlated with pH, base excess, lactate levels, and the conventional fibrinolytic markers (ie, PLG, α_2-PI, and t-PA activity). Study participants were assigned to 4 groups according to the severity of fibrinolysis (very strong $\leq$ 1107 seconds, 1107 seconds < strong $\leq$ 1961 seconds, 1961 seconds < moderate $\leq$ 3397 seconds, and weak > 3397 seconds) based on the LOT quartile, which was an indicator of fibrinolytic severity in the EXTEM tests. According to the severity of fibrinolysis, activity levels of t-PA gradually increased, and PLG and α_2-PI levels gradually

Table 3. Spearman Correlation of Fibrinolytic Variables Based on the EXTEM Test in Patients With Cardiac Arrest.

Characteristics, thromboelastometry, and conventional laboratory tests	EXTEM		
	LI 30	LOT	LT
Age, year	0.006	0.097	0.073
Duration of cardiac arrest, minutes	0.072	0.054	0.019
Blood gas analysis			
pH	0.550[a]	0.534[a]	0.544[a]
Base excess, mmol/L	0.392[b]	0.389[b]	0.426[b]
Lactate, mmol/L	−0.506[a]	−0.486[a]	−0.487[a]
EXTEM			
Lysis index at time 30 minutes, %	NA	0.906[a]	0.919[a]
Maximum lysis, %	0.097	0.080	0.167
Lysis onset time, seconds	0.906[a]	NA	0.992[a]
Lysis time, seconds	0.919[a]	0.992[a]	NA
Conventional laboratory tests			
Fibrinogen, mg/dL	0.640[a]	0.694[a]	0.719[a]
Fibrinogen/fibrin degradation products, μg/mL	0.083	0.082	0.117
Plasminogen, %	0.459[a]	0.533[a]	0.543[a]
α_2-plasmin inhibitor, %	0.359[b]	0.427[b]	0.442[a]
Plasmin-α_2-plasmin inhibitor complex, μg/mL	0.130	0.007	0.033
Total plasminogen activator inhibitor, ng/mL	−0.108	−0.081	−0.129
Prothrombin time, seconds	−0.462[a]	−0.594[a]	−0.616[a]
Tissue-plasminogen activator, IU/mL	−0.500[a]	−0.565[a]	−0.581[a]

Abbreviations: EXTEM test, the extrinsic coagulation test that is primed using rabbit brain tissue factor; LI 30, lysis index at time 30 minutes; LOT, lysis onset time; LT, lysis time; NA, not available.
[a] $P < .01$.
[b] $P < .05$.

decreased; these correlations were statistically significant. However, the PAI levels did not change, regardless of the severity of fibrinolysis (Figure 1).

Discussion

In this study, significant hyperfibrinolysis was diagnosed by ROTEM in all patients with OHCA. Patients with OHCA exhibited an approximately 200-fold higher level of t-PA activity and lower level of α_2-PI than participants in the control group. The PAI level was not elevated in patients with OHCA. The severity of fibrinolysis observed using ROTEM correlated with the elevation of t-PA activity and decrease in α_2-PI. The hyperfibrinolysis observed with thromboelastometry was probably attributable to the large amount of active t-PA and a consumptive decrease in α_2-PI in blood samples obtained from patients with OHCA.

The severity of fibrinolysis in the EXTEM tests correlated with t-PA activity. It was reported that whole-body ischemia/reperfusion and tissue hypoxia, owing to cardiac arrest, resuscitation, and subsequent ROSC, induced a substantial release of t-PA from Weibel-Palade bodies in endothelial cells.[24,25] In this study, a marked elevation of t-PA induced the consumptive reduction of PLG and α_2-PI and an increase in PIC. Furthermore, the active t-PA in the blood sample would have converted PLG to plasmin and induced hyperfibrinolysis in the measurement cup when ROTEM measurements were commenced postconsumption of α_2-PI.

In this study, the PAI level was not elevated in patients with OHCA. However, previous studies showed that the PAI level increased in patients with OHCA.[2,4,26] The difference between our results and those of previous studies[2,4,26] may be explained by the difference in the timing of blood sampling. Previous studies showed that PAI gradually increased from a time point immediately after ROSC to $\geq$24 hours post-ROSC.[2,4,26] In a hypoxic animal model, the PAI messenger RNA and PAI antigens increased after 16 hours following the induction of hypoxia.[27] Therefore, as blood samples in our study were taken on arrival at the hospital, it is likely that the PAI levels had not yet begun to increase.

Both FDP and PIC are frequently used as conventional indicators of fibrinolysis; however, they did not correlate with the fibrinolytic parameters of the EXTEM test in the present study. Elevation of the FDP and PIC levels indicates the occurrence of fibrinolysis prior to blood sampling. Even with high levels of FDP and PIC, fibrinolysis does not always occur in ROTEM measurements because t-PA may have been completely exhausted in the blood sample. Therefore, FDP and PIC mainly are indicators of past status and do not always indicate current and future conditions. Moreover, high levels of FDP and PIC cannot induce hyperfibrinolysis in an EXTEM test.

In previous studies, maximum lysis, LOT, lysis time, and lysis index at time 30 minutes were used to indicate fibrinolysis in ROTEM.[17-21,28] Although maximum lysis was the most frequently used thromboelastometric parameter to evaluate hyperfibrinolysis,[10,11,17,18,21] the present study shows limited utility of maximum lysis because of a ceiling effect as it reaches 100% in almost all patients. The LOT is a continuous scale and was reported to exert a higher discriminative level in the presence of high t-PA concentrations than maximum lysis.[19] In this study, we could not distinguish the severity of fibrinolysis in each patient because maximum lysis reached 100% in almost all the patients. Therefore, we used LOT as the main indicator of fibrinolysis in ROTEM.

In the clinical settings, both during and after cardiopulmonary resuscitation, patients with OHCA frequently undergo invasive procedures, such as extracorporeal cardiopulmonary resuscitation and percutaneous coronary intervention. Moreover, hemorrhagic complications are occasionally observed. Therefore, it is important to understand and evaluate the hyperfibrinolytic mechanisms after a cardiac arrest. Furthermore, although the results of t-PA measurements cannot be promptly derived, the LOT in ROTEM can promptly detect hyperfibrinolysis.[19]

This study has some limitations. We evaluated a small number of patients in a single center. Furthermore, the causes of cardiac arrest were diverse, including cardiac disease, asphyxia, and subarachnoid hemorrhage, and the results may differ according to the causes of cardiac arrest.

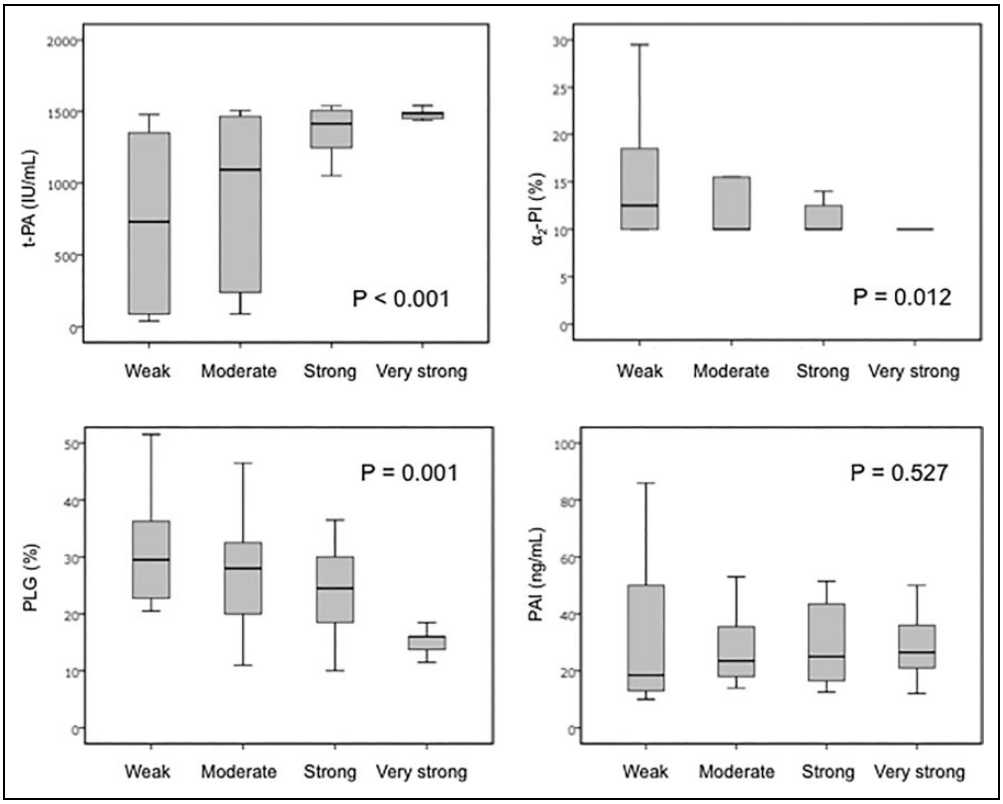

Figure 1. Relationship between conventional fibrinolysis markers and the severity of fibrinolysis. Patients with OHCA were divided into 4 groups (weak, moderate, strong, and very strong) according to the severity of fibrinolysis by using the quartile of lysis onset time (LOT). Conventional markers of fibrinolysis, such as the tissue-plasminogen activator (t-PA), α_2-plasmin inhibitor (α2-PI), plasminogen (PLG), and total plasminogen activator inhibitor (PAI), were compared in each group by using the Jonckheere-Terpstra test. Strong fibrinolysis in EXTEM was associated with a strong elevation of t-PA and a decreased levels of PLG and α2-PI; however, there was no change in the PAI.

In conclusion, hyperfibrinolysis was frequently diagnosed by ROTEM in patients with OHCA, and the fibrinolysis parameters of EXTEM correlated with conventional fibrinolysis markers. Hyperfibrinolysis in ROTEM correlated with the elevation of t-PA and the decrease of α2-PI. The FDP and PIC increased in patients with OHCA, but this increase was not related to hyperfibrinolysis in ROTEM. The PAI level was not related to the severity of fibrinolysis.

Authors' Note

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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